# GENERAL HYPOTHERMIA FOR EXPERIMENTAL INTRACARDIAC SURGERY*

## THE USE OF ELECTROPHRENIC RESPIRATIONS, AN ARTIFICIAL PACEMAKER FOR CARDIAC STANDSTILL, AND RADIO-FREQUENCY REWARMING IN GENERAL HYPOTHERMIA

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GENERAL HYPOTHERMIA is being investigated as a means of reducing the oxygen requirements of the body sufficiently to allow exclusion of the heart from the circulation, thereby permitting intracardiac surgery under direct vision.

During the last two years, an interdepartmental research team has studied oxygen transport and utilization in dogs at low body temperatures[1] and has investigated the factors governing survival in hypothermia.[2] A total of 176 dogs have been cooled. Continued improvement in our technic of cooling and re-warming has made reduction of body temperature to 20°C in dogs a relatively safe procedure. However the minimal temperature with survival has been 15°C. There are no ill effects from cooling to 20°C. Death at lower temperatures is usually due to ventricular fibrillation. Below 28°C the animal enters a state of "cold narcosis" in which an anesthetic agent is no longer necessary to maintain unconsciousness and relaxation. At 20°C the oxygen consumption, cardiac output, blood pressure and heart rate are about 15 per cent of normal. With the knowledge that hibernating mammals of similar normal anatomy can survive body temperature of 3°C,[3] we have been encouraged to seek a method of reducing temperatures in dogs below the present critical level.

### COOLING WITH "ELECTROPHRENIC RESPIRATION"

The present method of cooling, using two blankets containing coils with circulating refrigerant** has already been described.[1, 2] The animals are given digoxin and procaine intravenously initially and hypothermia is then induced with the aid of intravenous pentothal and curare to control shivering. About half of the animals have been heparinized with no recognizable effects on the

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cooling pattern. Venesection is used for abnormal increase in venous pressure. Continuous cathode-ray electrocardiograph visualization is used.*

Recently artificial respiration, necessary at lower body temperature, has been carried out by the periodic stimulation of the exposed phrenic nerve, as described recently[4] as the "electrophrenic respiration." A stimulator† with a rotating potentiometer‡ has been used as an electrical source. This device delivers any type of electrical current in periodic bursts of desired duration or frequency. The respiratory rate is varied simply by adjusting a dial.

This technic has been used 30 times. Continuous venous pressures from the superior vena cava have been observed in each experiment. Electrophrenic respirations applied in the presence of a positive venous pressure have invariably caused a reduction, and pressures below zero cm. of water have been maintained in nearly all animals.

One phrenic nerve only is stimulated. Optimum results are obtained when the stimulating electrode is in contact with all roots of the nerve, at which time an excellent respiratory excursion is obtained which easily maintains full arterial oxygen saturation. In the dog which has normally a communication between pleural cavities these diaphragmatic movements are of no value with the chest open. At such times positive pressure respirations are instituted.

### EXCLUSION OF THE HEART AND CARDIOTOMY

It has been possible at a body temperature of 20°C to exclude the heart from the circulation for periods of 15 minutes with survival. In some of the animals during the period of exclusion the heart has been opened and then sutured.

Although further physiologic studies are in progress and methods of cooling are being investigated which may allow reduction of the body temperature with safety to below 20°C, it was decided to test our hypothesis by operating at this temperature. Using sterile technic the fifth rib is removed and the chest opened. Bull dog clamps are applied to the superior and inferior venae cavae and azygos vein. This prevents all blood from entering the heart except that from the mouth of the coronary sinus, which is reduced to a slow ooze because of the low arterial pressure.

No attempt has been made to carry out intracardiac procedures or investigate special exposures. The cardiotomy performed is a token operation. Once the heart is excluded from the circulation, the pericardium is incised and after surface application of cocaine the right auricle is opened with exploration of right auricle and ventricle. Several technics have been used to attempt to eliminate or minimize air embolism. Usually during closure of the cardiac muscle the chambers are filled with heparin-saline solution. With

* Smith and Stone, Ltd., Georgetown, Ontario.
† Grass Instrument Co., Quincy, Mass., U. S. A.
‡ National Research Council, Ottawa, Canada.

completion of the cardiotomy the clamps are removed and the chest closed. Re-warming is commenced immediately.

When the clamps are applied, the heart appears empty and the auricle no longer fills in diastole. Its rate, reduced by hypothermia to 20 per minute, usually increases four or five beats per minute. Incision into the auricle is well tolerated and has never precipitated ventricular fibrillation.

In 39 dogs the heart has been excluded from the circulation in the manner described for periods of 15 minutes or more at a body temperature of 20°C. On 23 of these a cardiotomy was performed. Nineteen, or 49 per cent of the

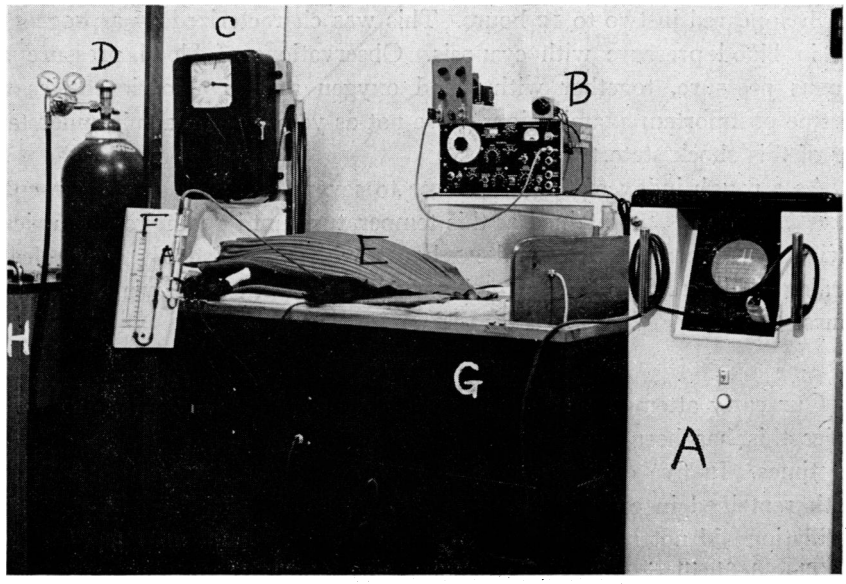


FIG. 1

A. Continuous cathode-ray electrocardiograph.
B. Electric stimulator.
C. Thermometer.
D. Oxygen tank.
E. Animal wrapped in cooling blankets containing coils of circulating refrigerant at 0°C.
F. Venous pressure and blood pressure Manometers.
G. Diathermy re-warming cabinet (lower half).
H. Refrigerating machine.

total, died either during the clamp-off period or during re-warming. Twenty, or 51 per cent of the total (including 11 with cardiotomy) were revived to normal body temperature.

Of those dying in the cold state, five experienced cardiac standstill, while the remaining 14 died from ventricular fibrillation. Six deaths occurred during the clamp-off period, six immediately after removing the clamps and seven during re-warming. Some of the deaths immediately after removal of the clamps may have been caused by removing the clamps too rapidly, with

overfilling of the heart. Most of the deaths in the re-warming period occurred around 32°C.

Of the 20 animals revived to normal body temperature and returned to their cages, six survived the procedure completely. Of these, two were sacrificed during the second week because of gross wound infection and the remaining four were used several weeks later for other cooling experiments. After an initial period of lethargy and weakness, these animals resumed apparently normal activity within a few days.

The remaining 12 with good respiratory function and normal electrocardiograph tracings at normal body temperature developed a state of shock which appeared in two to 12 hours. This was characterized by a progressive fall in blood pressure with cyanosis. Observations of blood pressure and venous pressure, together with blood oxygen and hematocrit studies and routine postmortem examinations, have not as yet given us a full understanding of this shock state.

As a rough index of their tolerance to severe cold two dogs were cooled to 20°C and were maintained at this temperature until death from ventricular fibrillation. They lived 17 and 20 hours with a persistently good electrocardiographic tracing. Their total periods of hypothermia were 27 and 28 hours.

### DEFIBRILLATION

Our early attempts at defibrillation have been reported.[2] In the present series this has been attempted in ten experiments and has been successful six times. In five of these cases spontaneous heart beat returned, but the sixth remained in cardiac standstill. Those hearts with a weak ventricular fibrillation did not respond, or responded poorly to defibrillation.

The defibrillating shock is delivered to the heart through nickel-plated electrodes mounted upon an insulated handle after the method of Hooker, *et al.*,[5] Beck and Mautz,[6] using 50 to 120 volts, and frequencies of 25 to 60 cycles per second.

### AN ARTIFICIAL PACEMAKER FOR CARDIAC STANDSTILL

Medical men have little fear of temporary cessation of respiration and successfully apply artificial respiration in several forms for prolonged periods. With evidence that many hearts, including those in the hypothermic state, which have ceased beating still have the power to contract following mechanical stimulation,[7] it seemed reasonable to consider the use of an artificial pacemaker to restore heart function. It was felt that, using the principle of electrophrenic respiration, periodic electrical stimulation of S-A nodal area might restore the beat. This could conceivably be carried out for prolonged periods until the organism had been restored to a state where spontaneous normal heart action was regained. As yet no report of a similar technic used in the intact animal has been found in the literature.

This is a very early report of such a procedure which has been attempted recently in four cases of cardiac standstill, in each case with restoration of heart action. The stimulator, with rotating potentiometer, has been used to deliver impulses at any desired rate. An indifferent electrode is clipped onto the chest wall and the stimulating electrode placed in the region of the S-A node. Normal appearing heart action is observed and the heart rate is varied within limits by adjusting a dial.

In two experiments the artificial pacemaker was used for ten to 15 minutes, and when it was discontinued the heart returned to standstill. In the other two animals following electrical control of the heart beat for ten and 30 minutes, normal spontaneous heart beats returned.

In one of these following cardiotomy at 20°C the heart was sutured and clamps removed. Ten minutes later in the presence of good vigorous heart action and normal venous pressure, ventricular fibrillation set in. The heart was defibrillated by the technic described, producing cardiac standstill. Electrical stimulation of the S-A nodal area was then carried out for ten minutes, testing effect of withdrawal of this at intervals until spontaneous heart action was restored. The chest was closed and the dog re-warmed to normal body temperature, only to die several hours later.

Defibrillation following cardiac massage has been used to revive animals[8] and human beings,[6] and we have used cardiac massage for periods up to ten minutes, with return of normal heart action and revival. However, the possible advantages in hypothermia where the stimulating wire could be left in place during closure of chest and re-warming are obvious. Should such a technic prove worthwhile, its extension to other clinical conditions with cardiac arrest might be considered.

### RADIO-FREQUENCY REWARMING

Radio-frequency re-warming has been used successfully on hypothermic animals. Until recently, re-warming has been carried out by immersion of the animal in a water bath at a temperature of 40°C. Such a technic, although successful, has the theoretical disadvantage of re-warming superficial structures before the heart and blood stream. It was considered to have several unsatisfactory features, should hypothermia ever come to be applied to surgery on human beings.

Since 1900, short wave diathermy has been used extensively to study the production of hyperthermia from normal body temperature.[9] More recently, microwave diathermy has been used in similar investigations.[10] No reference has been found to their use in deep hypothermia. In our re-warming experiments, ordinary microwave and short wave capacitive heating diathermy technics were found unsatisfactory, due either to localized or inadequate general heating, or to electrode burns. Further investigation indicated that inductive heating was a preferable technic, providing greater facility of application, reduced danger of superficial burning, and more generalized heating. In this

type of heating, eddy currents are set up in the tissue within the influence of the electro-magnetic field of the induction coils. The heating action is caused by the conversion of the eddy currents to heat within the tissues. Since the vascular tissues produce a greater concentration of eddy currents our coils were arranged so as to parallel the main blood vessels, thus enhancing heat distribution throughout the body.

No optimum frequency was found within the usual short wave diathermy range. The rate of re-warming at 27 mc and 13 mc was about the same. However, at the lower frequency, the danger of coil burns was reduced.

A shielded radio-frequency heating cabinet was constructed along the lines of a conventional hyperthemia cabinet, with supplementary air heating to minimize heat losses by conduction. With this cabinet nine animals have been re-warmed and all successfully returned from an initial 15° to 20°C to normal body temperature. The rate of re-warming has varied between 3°C and 13°C per hour as a result of variation in experimental technic. The first two, imperfectly insulated, suffered extensive superficial burns, two others had a local reaction about the metal electrocardiographic electrodes, and five were free of any apparent ill effects.

At the present time a frequency of 14 megacycles is under study with induction coil-type applicators. This method is simpler than water immersion and allows easier access to the animal. It is felt that a satisfactory and safe technic is being developed, although an assessment of possible late ill effects is not yet possible.

## DISCUSSION

At normal body temperature of 38°C a dog will survive exclusion of its heart from the circulation from five to nine minutes.[11] Although the final survival rate of 15 per cent in this study following 15 minute exclusion of the heart at low body temperature is not very impressive, 85 per cent survived the actual clamp-off period. This suggests that our basic hypothesis may be correct.

With a greater knowledge of the physiology of hypothermia it may be possible to endow non-hibernating mammals with the ability to survive even lower temperatures than those tolerated thus far. Temperatures below 20°C would further reduce the tissue oxygen requirements and would conceivably increase the length of time an animal could tolerate interruption of its circulation. Should deep hypothermia be developed as a safe surgical technic, it might be expected to extend the scope of surgery in other fields.

Reference has already been made[2] to the many problems that must be solved to understand even the elementary changes in hypothermia. One is encouraged in this study, however, by our knowledge of the tolerance to cold exhibited by hibernating animals and the reports of human survival from temperatures as low as 25°C.

SUMMARY

1. It has been possible to exclude the heart from the circulation for periods of 15 minutes in dogs at a body temperature of 20°C with survival. In most of these animals during the period of exclusion the heart has been opened and then sutured. This procedure is attended by a high mortality and the cause of death is not clearly understood.

2. Periodic electrical stimulation of the phrenic nerve has been used as a form of artificial respiration during the period of respiratory depression in the lower temperature range.

3. Electrical defibrillation of the heart has been practiced.

4. An artificial pacemaker in the form of periodic electrical stimulation of the S A node area of the heart has successfully restored heart action in cardiac standstill in the cold state.

5. Radio frequency re-warming procedures have been studied.

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DISCUSSION.—DR. WILLIAM L. RIKER: We have enjoyed this paper very much, and wish to present some of the clinical applications of hypothermia. For the past two years at the Children's Memorial Hospital in Chicago, we have been interested in reducing the temperature of patients undergoing major surgical procedures, for two reasons. In the first place, we want to control hyperpyrexia. In more than a hundred